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Invited Review

Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence

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HIGHLIGHTS

- Genital powder use shows a weak association with ovarian cancer risk.
- The increase in absolute risk of ovarian cancer is very small.
- Body powders have different ingredients that can be hard to quantify.
- The causal mechanism underlying the observed associations is not clear.

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ABSTRACT

Many women apply powder to the genital area as a drying agent. Talc, an inert mineral with a high capacity to absorb water, has historically been a major component of body powders. Due to its similarity and co-occurrence with asbestos, the association of body powder/talc use and gynecological cancer risk, specifically ovarian cancer risk, has been a long-standing research question. Retrospective case-control studies have shown associations between genital powder use and ovarian cancer risk, with summary relative risk estimates from meta-analyses and pooled analyses ranging from 1.24 to 1.35 for ever versus never use. In contrast, prospective cohort studies have not shown a statistically significant association until recently, when a pooled analysis of four large cohorts demonstrated a weak, but statistically significant association among women with patent reproductive tracts (hazard ratio 1.13). Taken together, the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer. The causal factors underlying this association are not clear. Proposed factors include talc, other minerals, such as asbestos or quartz, that are known carcinogens and may contaminate talc products, or other powder ingredients that could cause inflammation of the reproductive tracts. Given the rarity of ovarian cancer in the general population, the small increase in relative risk translates to a very low increase in absolute risk. Further research is needed to understand the underpinnings of the observed association between genital powder use and ovarian cancer risk.

Contents

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1. Introduction

Talc is a soft and inert mineral with a high capability to absorb water and organic matter. It is used in a wide range of products, including paper, plastics, paint, rubber, agricultural products, pharmaceuticals, and cosmetics [1]. Because of its capacity to bind water, talc powder has been used in baby powders and feminine hygiene products as a drying agent. Notably, talc shares chemical features and often co-occurs with asbestos, a long-established carcinogen [2]. Due to the similarity with asbestos, talc has been evaluated for its carcinogenic potential [1]. Powder application to the genital area has been fairly common, but body powders contain varying levels of talc, including some labeled as talc-free [3]. Historically, there has been great interest in whether there is a link between genital talc use and cancers of the female reproductive tract.

The assessment of the carcinogenic potential of a biological or chemical agent is based on multiple lines of evidence from diverse studies, including epidemiological studies, mechanistic studies, cancer bioassays, and animal experiments. This review focuses on epidemiological data, particularly on studies evaluating the association between body powder/talc and ovarian cancer.

In 1971, Henderson et al. showed talc particles in 10 out of 13 ovarian cancer tissue samples, as well as in a low number of endometrial and cervical cancer tissues [4]. In 1979, Longo and Young summarized the evidence available at the time for a role of talc in ovarian cancer and laid out what studies would be needed to better assess the relationship [5]. In 1982, Cramer et al. published the first epidemiological study evaluating the association between genital talc use and ovarian cancer [6]. In a case-control study conducted in the Boston area, the authors reported an increased risk of ovarian cancer (OR 1.92; 95% CI 1.27–2.89) for any perineal exposure to talc. Since then, several case-control studies evaluating the association between talc or body powder and ovarian cancer have been published that showed positive associations, while evaluations in prospective cohort studies have shown only weak or no associations (summarized in Table 1). Associations between talc use and uterine cancer have also been investigated in several case-control and cohort studies.

In 2010, IARC published volume 93 of their Monograph series on "Evaluation of Carcinogenic Risks to Humans" that included the assessment of carcinogenicity of carbon black, titanium dioxide, and talc [1]. Based on the summary of the biological and epidemiological data at the time, the IARC group classified talc as a possible carcinogen (2B), which means that there is some evidence that a substance can cause cancer in humans, but that the evidence was not conclusive. Since the 2010 IARC carcinogenicity assessment, several epidemiological studies have been published that expand the state of knowledge about talc's possible carcinogenicity. In this review, we evaluate the epidemiological evidence on whether there is an association between body powder use and ovarian cancer risk. If the evidence suggests an association between powder use and ovarian cancer, it is important to understand underlying causal factors and the potential clinical and public health relevance.

2. Chemical properties of talc in body powder

Talc may either refer to mineral talc itself, or to cosmetic products that contain mineral talc in varying proportions, often in combination with corn starch. Talc is a metamorphic mineral composed of magnesium silicate (generalized chemical formula $Mg_3Si_4O_{10}(OH)_2$). Mineral talc is commonly platy, i.e. it occurs in flaky layers or sheets, but it can also occur as asbestiform fibers. Talc is the softest known mineral. Solid talc minerals are crushed into a white powder referred to as talcum powder that has great ability to absorb both watery and oily substances. This form of talc is the focus of the current review.

Talc can be contaminated with a variety of other minerals. Most important are contaminations with asbestos or quartz, both class 1 carcinogens according to IARC (which means that there is enough evidence to conclude that these substances can cause cancer in humans), which frequently co-occur naturally with talc [7]. Early cosmetic talc products were found to be contaminated with asbestos to various extent [8]. More stringent quality control introduced in talc production in 1976 led to a steep reduction in asbestos contamination. While talc products since the 1980s have been considered asbestos-free, recent reports have suggested that low-level contamination of talc with asbestos fibers may have persisted in some cosmetic products. To systematically assess the presence of asbestos in cosmetic products, the US FDA recently conducted extensive testing of cosmetic talc products and identified several products with asbestos contaminations that have subsequently been recalled from the market [9]. It cannot be excluded that other ingredients of body powders, such as corn starch, may also have biological effects, e.g. by causing irritation or inflammation of the female reproductive tract.

3. Biological properties of talc and carcinogenicity studies

The number of biologic and animal studies evaluating the carcinogenic potential of talc is limited. In autopsy studies, talc particles have been found in the lungs of occupationally exposed individuals [10]. Pathology studies have shown talc particles in various cancer tissues including stomach tumors and gynecological tumors, suggesting that talc can reach various parts of the body through inhalation, deposition, and even retrograde movement in the female genital tract [1]. Potential toxic effects of talc may depend on the route and dose of administration. When conducting carcinogenicity assessment, it is important to distinguish effects caused by other contaminating minerals such as asbestos or quartz, from talc-specific effects. This distinction is only possible when highly pure substances are studied.

The carcinogenicity of talc has been evaluated in few animal studies, summarized in the IARC monograph [1]. For example, mice were

Table 1
Reported estimates of the association between ever (versus never) powder use and ovarian cancer, including summary estimates from published meta- and pooled analyses.

Author	Year	OR (95% CI)	Meta-analyses			Pooled analyses			Comments
			Penninkilampi 2018	Berge 2018	Taher 2019	Terry 2013	O'Brien 2020[a]	Davis 2021[b]	
Overall summary estimates			1.31 (1.24–1.39)	1.22 (1.13–1.3)	1.28 (1.2–1.37)	1.24 (1.15–1.33)	1.08 (0.99–1.17)	1.32 (1.17–1.48)[c]	
Case control summary estimates			1.35 (1.27–1.43)	1.26 (1.17–1.35)	1.32 (1.24–1.40)	1.24 (1.15–1.33)			
Cramer	1982	1.92 (1.27–2.89)	X	X	X				
Hartge	1983	2.5 (0.7–10)	X	X	X				Meta-analyses used different subgroup estimates
Whittemore	1988	1.4 (1.98–2)	X	X	X				
Booth	1989	1.3 (0.94–1.8)	X	X					
Harlow	1989	1.1 (0.7–2.1)	X	X	X				
Chen	1992	3.9 (0.9–10.6)	X	X					
Harlow	1992	1.5 (1–2.1)		X	X				
Rosenblatt	1992	1 (0.2–4)	X	X	X				Meta-analyses used different subgroup estimates
Tzonou	1993	1.05 (0.28–3.98)	X	X	X				
Purdie	1995	1.27 (1.04–1.54)	X	X					
Shushan	1996	2 (1.11–3.6)	X						
Green	1997	1.3 (1.06–1.6)	X		X				
Chang	1997	1.42 (1.08–1.86)	X	X	X	X			
Cook	1997	1.5 (1.1–2)	X	X	X				
Godard	1998	2.49 (0.94–6.6)	X	X	X				
Wong	1999	0.92 (0.24–3.57)	X	X	X				
Ness	2000	1.5 (1.1–2)	X	X	X				
Mills	2004	1.37 (1.02–1.85)	X	X	X				
Goodman	2008	0.99 (0.7–1.41)		X		X			Abstracted numbers from Terry 2013
Merritt	2008	1.17 (1.01–1.36)	X	X	X	X			
Gates	2008	1.06 (0.89–1.28)			X				Data updated by Gates 2010 and Cramer 2016
Moorman	2009	1.37 (1.05–1.8)		X	X	X		X	Abstracted numbers from Terry 2013
Rosenblatt	2011	1.27 (0.97–1.66)	X	X	X	X			
Lo-Ciganic	2012	1.34 (1.07–1.66)		X		X			Abstracted numbers from Terry 2013
Kurta	2012	1.4 (1.16–1.69)	X		X				
Wu	2015	1.46 (1.27–1.69)	X	X	X	X		X	
Cramer	2016	1.33 (1.16–1.52)	X	X	X	X			Update of Gates 2010
Schildkraut	2016	1.44 (1.11–1.86)	X	X	X			X	
Cohort summary estimates			1.06 (0.9–1.25)	1.02 (0.85–1.2)	1.06 (0.9–1.25)		1.08 (0.99–1.17)		
Gertig	2000	1.09 (0.86–1.38)	X		X		X		Updated in Gates 2010, updated numbers in O'Brien 2020
Gates	2010	1.06 (0.89–1.28)		X			X		
Houghton	2014	1.12 (0.92–1.36)	X	X	X		X	X	Updated numbers in O'Brien 2020
Gonzalez	2016	0.73 (0.44–1.21)	X	X	X		X		Updated numbers in O'Brien 2020

[a] Additionally includes data from the Nurses' Health Study II (talc data unpublished)
[b] Additionally includes data from the Cook County Case-Control Study (talc data previously unpublished).
[c] OR = 1.22 (95% CI: 0.97–1.53) in African-American women; OR = 1.36 (95% CI: 1.19–1.57) in White women.

subjected to inhalation, as well as subcutaneous, intraperitoneal, and intrathoracic injection. Generally, no increase in tumor incidence was observed in mice. Rats were subjected to oral administration, inhalation, as well as intraperitoneal, intrathoracic, or intrapleural injection, and ovarian implantation. In some studies, incidences of alveolar and bronchial carcinomas were increased after talc inhalation. An increase in pheochromocytomas was also observed, but the IARC group did not consider that pheochromocytomas are causally related to talc. Hamsters were subjected to inhalation and intratracheal injection; no tumors were observed in these studies. A study conducted in rats that evaluated intravaginal and perineal talc application did not observe any neoplastic changes, but inflammatory reactions in the fallopian tubes and other areas of the genital tract [11]. However, the limited follow-up time may have precluded development of tumor endpoints.

Several lines of evidence suggest that talc causes inflammatory reactions. Animal studies have shown release of cytokines, chemokines and growth factors from pleural mesothelial cells after injection with talc. Similarly, in human tissue, intrapleural talc injection has led to inflammation and pleural fibrosis. In patients with documented perineal talc use, talc particles can be found in multiple sites along the female reproductive tract [12]. Talc use was shown to have an inverse association with MUC1 antibodies in healthy women, but the biologic process underlying this association is not understood [13]. One study found a higher risk of ovarian cancer associated with powder use among women with variations in the GSTM1 and GSTT1 genes [14], but to our knowledge, no other studies have examined potential gene-by-environment interactions.

4. Important considerations for epidemiological studies of talc use and gynecological cancer risk

4.1. Etiologic heterogeneity of ovarian cancer

Ovarian cancer is characterized by profound heterogeneity that can be observed in site of origin, genetic susceptibility, somatic mutations, molecular pathways, risk factor associations and morphologic differences [15–17]. In aggregate, these data suggest that there are several etiologically distinct types of cancers that manifest in the ovaries. It has been proposed that a majority of high-grade serous carcinomas arise from the fallopian tubes, while endometrioid carcinomas may arise from orthotopic or ectopic endometrial tissue, including endometriosis tissue [15]. Many ovarian cancer risk factors and exposures are specific to certain subtypes [16]. Demonstrating a subtype-specific association can, theoretically, point to a specific carcinogenic effect.

Further, there is similarity between subtypes of ovarian and endometrial cancers [18]. Serous ovarian and endometrial carcinomas have similar molecular features and may originate from the same cells in the fallopian tube. Similarly, endometrioid ovarian carcinomas share risk factors and molecular features with endometrioid endometrial carcinomas [16,19,20]. Therefore, comparisons of subtype-specific associations across gynecologic cancer sites can inform the carcinogenic process.

4.2. Study designs

Epidemiological studies of talc exposure have been conducted in special populations, like talc miners and pulp and paper industry workers who are exposed to high doses of talc over an extended time period. These occupational studies allow for the assessment of very high levels of exposure that are typically not found in the general population, with possibilities for detailed studies of dose-response effects (duration and frequency). However, due to the possible contamination of talc with co-existing minerals in mines and in industrial talc products, evaluating talc-specific effects remains a challenge. Ovarian cancer is particularly difficult to study in occupational settings, as high-exposure jobs are typically male-dominated.

In the general population, epidemiological studies of talc use and gynecological cancer risk include case-control studies and prospective cohort studies. A case-control study is an observational study consisting of a group of cases who experienced a specific outcome, such as ovarian cancer, as well as controls without that outcome [21,22]. These are compared to see if there are differences in exposure patterns between the two groups. Controls for case-control studies should be sampled from the base population from which the cases arise. Incompatibility between the controls and the true source population can lead to bias, as discussed further below. In contrast, cohort studies are observational studies that follow an initially non-diseased population to see who develops the outcome(s) of interest [23]. Cohort studies are typically much larger than case-control studies and require long-term follow-up, especially for rare outcomes.

These study designs have different advantages and disadvantages. The major difference between case-control studies and cohort studies is that case-control studies assess exposures at the time of or just after a cancer diagnosis, which can lead to differential reporting of exposures by cases and controls. In contrast, exposure assessment in cohort studies occurs before the cancer diagnosis. Case-control studies typically focus on a single disease of interest, like ovarian cancer, and are specifically designed to evaluate the exposures of interest for that specific disease. Therefore, case-control studies tend to have more detailed information on specific exposures. In contrast, cohort studies generally evaluate a wide range of disease outcomes. Exposure assessment is much broader and usually does not go as deep into specific exposures. For genital powders, this means studies will typically have less information on mode of application, dose, and duration. Further, when exposure assessment is not re-assessed at later follow-up times in cohort studies, the exposure assessment may refer to a time period that was many years, if not decades, prior to disease development, thereby opening the possibility to non-differential misclassification.

For rare diseases, cohort studies must be of sufficient size and duration to allow for well-powered assessment of potential risk factors. Most individual prospective cohort studies have not observed meaningful associations between talc use and ovarian cancer risk. However, many cohort studies have few cases and may not be sufficiently powered to detect a small increase in risk at statistically significant levels. It is important to be transparent about study power and the lower limit of detectable associations when reporting study results.

Both case-control studies and cohort studies typically report relative risk measures, including odds ratios or hazard ratios. These relative risks indicate how much the risk of an outcome is increased due to a specific exposure in one group compared to another. Measures of absolute risk of disease may have greater clinical relevance but are often difficult to assess using these standard study designs. Disease prevalence is a key factor here: the rarer the disease, the smaller the absolute risk increase for a given relative risk increase [24]. Accordingly, for a rare disease like ovarian cancer, even a large relative increase may not translate to an increase in absolute risk that is considered clinically meaningful.

4.3. Bias and confounding

In contrast to randomized trials, which are designed to achieve unbiased assessment of specific exposures, drugs, or interventions, observational studies are at risk of bias. In epidemiology, bias is defined as an error in the study design or conduct that leads to results that are systematically different from the truth [25]. Key forms of bias including selection bias, information bias, and confounding. Selection bias is introduced when there is a systematic difference between study participants and the base population, or a systematic difference between cases and non-cases. Information bias may occur when data on exposure or outcomes is systematically different between cases and non-cases. This includes recall bias, discussed in further detail below, and survivor bias, which could occur if talc use affected survival time. Survivor bias is a potentially important source of bias for retrospective studies of diseases with high fatality rates, such as ovarian cancer, as cases need to live long enough to be included. If cases are not interviewed soon after their diagnosis, the sample may include a disproportionate number of women with less severe disease.

Confounding occurs when an exposure is associated with an outcome, but the causal association is driven by a different factor that is correlated with both the exposure and the outcome. If the confounding factor is well-measured, bias due to confounding can be mitigated by adjusting for or stratifying on that variable using multivariable regression models. As an example, the association between genital powder use and uterine cancer is strongly confounded by body mass index (BMI), which is both a risk factor for uterine cancer and a strong predictor of genital powder use. As shown by O'Brien et al., while crude estimates of the genital powder use- uterine cancer relationship indicated a strong positive association, models adjusted for BMI indicated there was no independent relationship between body powder use and uterine cancer [26].

4.4. Assessment and quantification of talc exposure

Since talc use is not documented in medical or pharmacy records, assessment of talc exposure relies purely on self-report [27]. Cosmetic talc products are typically not easily recognizable without studying the list of ingredients. Body powders have a wide range of ingredients with different talc content, including some talc-free varieties. Since many study participants may not know whether they used talc, questionnaires in epidemiologic studies often ask about body powder use. Some case-control studies include questions about the mode of application. Body

powder may be applied to the genital area directly or via application to sanitary napkins or diaphragms [1].

When evaluating associations between exposures and disease outcomes in epidemiological studies, establishing a dose-response relationship can be important to support a causal association. Due to the varying talc content of body powders and the different modes of application, it is difficult to estimate the actual talc dose applied to the genital area.

Despite these limitations, some case-control studies have assessed the frequency and duration of genital powder use. This allows researchers to distinguish groups with potentially higher and lower exposure, even when the absolute talc exposure level cannot be quantified. Cohort studies typically have collected less information on dose and frequency of application than case-control studies.

4.5. Recall bias

Since exposure assessment in case-control studies is conducted at the time of diagnosis, there is a risk of differential recall bias, a type of information bias. This occurs when reporting of an exposure is influenced by the diagnosis and affected individuals are more likely to report a specific exposure or are likely to report a higher dose or duration of exposure compared to control individuals. This differential recall bias may result in an association of an exposure with disease outcome when there is truly none, or it may lead to overestimation of a truly small association.

Differential recall bias has been observed in case control studies for a wide range of exposures, but there are specific and well-documented concerns that differential recall bias underlies some of the associations in case-control studies of talc use and ovarian cancer risk. For example, in a large case-control study of African American women conducted in North Carolina Schildkraut et al. reported a strong association between talc use and ovarian cancer [28,29]. However, they only observed a significant association between genital powder use and ovarian cancer in participants interviewed after 2014 (adjusted OR, 2.91; 95% CI, 1.70–4.97), a benchmark for when a possible talc–ovarian cancer association began being widely discussed in the media as a result of ongoing litigation. Prior to 2014, the association was weaker and not statistically significant (OR, 1.19; 95% CI, 0.87–1.63; P interaction by time period = 0.005). Importantly, the prevalence of genital powder use among controls was the same across the two time periods, whereas the proportion of cases reporting "any" genital powder use increased among those interviewed during the later time period. This suggests that differential recall of body powder use may explain at least some of the observed associations.

4.6. Confounding by indication

Confounding by indication is a concern in epidemiological studies evaluating drugs and other exposures. It can occur when an underlying cause of the outcome also causes changes to exposure. An example relevant to the powder-ovarian cancer association is if a hormone-related condition was a risk factor for ovarian cancer, and also altered the vaginal environment in a way that made women more or less likely to apply genital powder. Such a relationship would induce a non-causal association between talc use and ovarian cancer. Most studies do not collect data on the underlying reason for talc use, which may be wide ranging. Without this knowledge, we cannot rule out confounding by indication.

4.7. Timing of exposure

Talc/body powder may be used over a wide age range, or only during a short period in life. The biologic effect of body powder on the cells at risk of ovarian cancer may differ depending on the timing of exposure. With the example of ovarian and other cancers, the disease latency period may be quite long, meaning that use several decades prior could be associated with disease risk. On the other extreme, recent use could also be relevant, including as a promoter of pre-cancerous cells into tumors, or by accelerating the growth of existing tumors. Few studies have collected information on talc/body powder dose and duration during specific time windows or across the lifespan. Depending on how talc/body powder exposure is assessed, many studies may not evaluate the relevant exposure window.

5. Summary of the data for genital powder use and ovarian cancer risk

5.1. Overall associations reported in systematic reviews, meta-analyses, and pooled analyses

Over the last 15 years, several systematic reviews and meta-analyses evaluating the association between body powder or talc use and ovarian cancer have been published. Three recent meta-analyses and three pooled analyses are summarized in Table 1 [30–34]. A total of 32 papers were included in at least one of the meta-analyses and pooled analyses spanning articles from 1982 to 2016 [6,14,28,35–62]. There were some differences with regard to inclusion of studies and specific estimates which resulted in differences of the reported associations between the meta-analyses and the pooled analyses.

Penninkilampi and Eslick summarized 23 case-control studies and 3 cohort studies via meta-analysis [33]. Any perineal talc use was associated with increased risk of ovarian cancer (OR = 1.31; 95% CI: 1.24–1.39). An association with ever use of talc was found in the meta-analysis of case-control studies (OR = 1.35; 95% CI: 1.27–1.43), but not cohort studies (OR = 1.06; 95% CI: 0.90–1.25). The systematic review also evaluated lifetime applications of talc to assess whether there is a dose-response relationship. Subjects with more than 3600 lifetime applications (OR = 1.42; 95% CI: 1.25–1.61) had a slightly higher risk of ovarian cancer compared to those with <3600 applications (OR = 1.32; 95% CI: 1.15–1.50).

Berge et al. summarized 24 case-control studies and 3 cohort studies via meta-analysis [30]. The overall summary relative risk (RR) for ever use of genital talc and ovarian cancer was 1.22 (95% CI: 1.13–1.30). The RR for case-control studies was 1.26 (95% CI: 1.17–1.35) and for cohort studies was 1.02 (95% CI: 0.85–1.20, P-for-heterogeneity by study design = 0.007). There was a weak trend in RR with duration and frequency of genital talc use.

Taher et al. summarized 21 case-control studies and 3 cohort studies [31]. This was the most recently published meta-analysis, and the authors included a detailed comparison of included studies in their supplemental materials, with the main differences being the exclusion of studies that did not report talc use as main effect estimates in their original publication. A positive association between perineal use of talc powder and ovarian cancer was found (OR = 1.28; 95% CI: 1.20–1.37). They noted significant risks in Hispanic and White women, in women applying talc to underwear, in pre-menopausal women, and in post-menopausal women receiving hormonal therapy.

Terry et al. published a large pooled analysis from the Ovarian Cancer Association Consortium (OCAC) [34]. This pooled analysis included eight case-control studies that are included in the previously discussed meta-analyses. In contrast to meta-analyses, pooled analyses make use of the original data, with the ability to harmonize exposure categories and covariates across studies. Based on data from 8525 cases and 9859 controls, Terry et al. found that genital powder use was associated with a statistically significant increase in risk of ovarian cancer (OR = 1.24, 95% CI: 1.15–1.33). There was limited evidence of a dose-response trend across categories of lifetime number of applications (p-for-trend = 0.17).

O'Brien et al. pooled data from the four large prospective cohorts known to have information on genital powder use [32]. This included updated data from three previously published cohorts [14,40,42,48] as well as previously unpublished data from the Nurses' Health Study II. Ever use of genital powder was associated with a small but not

statistically significant increase in ovarian cancer risk (HR = 1.08, 95% CI: 0.99–1.17). There was no evidence that more frequent or long-term use was associated with further increases in risk.

Most recently, Davis et al. published results from a pooled analysis of 5 studies (4 population-based case-control, 1 prospective cohort) participating in the Ovarian Cancer in Women of African Ancestry Consortium (OCWAA) [63]. They observed a positive association between genital powder use and ovarian cancer in both African-American women (OR = 1.22, 95% CI: 0.96–1.55) and White women (OR = 1.34, 95% CI: 1.16–1.56 in White women), with a combined estimate of OR = 1.31 (95% CI: 1.15–1.48) overall. There were no clear dose-response trends.

5.2. Associations of genital powder use and ovarian cancer risk by histotype

As discussed previously, ovarian cancers encompass several different histotypes, which may have different cells of origin and unique risk factors. The identification of subtype-specific associations could strengthen the argument for the existence of a causal relationship. Most studies published since 1997 have included histotype-specific estimates, with serous ovarian cancers (sometimes restricted to high grade serious or invasive serous) being the most common (Table 2). In the previously published meta-analyses, Penninkilampi and Eslick reported that ever talc use was positively associated with serous carcinomas (OR = 1.32, 95% 1.22–1.43), including among cohort studies only (OR = 1.25, 95% CI: 1.01–1.55) [33]. Talc use was also positively associated with endometroid tumors (OR = 1.35, 95% CI: 1.14–1.60), and possibly mucinous (OR = 1.12, 95% CI: 0.94–1.33), but not clear cell (OR = 1.02, 95% CI: 0.75–1.39).

The Berge et al. meta-analysis reported similar findings, including a positive association between talc use and serous carcinoma (RR: 1.24; 95% CI: 1.15–1.34) and to a lesser extent endometroid carcinoma (RR: 1.15, 95% CI: 0.91–1.39), but not mucinous (RR = 0.96, 95% CI:

Table 2
Reported estimates of the association between ever (versus never) powder use and ovarian cancer by histotype, including summary estimates from published meta- and pooled analyses.

Author	Year	Serous	Endometroid	Mucinous	Clear cell	Meta-analyses			Pooled analyses		
						Penninkilampi 2018	Berge 2018	Taher 2019	Terry 2013[a]	O'Brien 2020[b]	Davis 2021[c]
Case control studies											
Harlow	1992	1.4 (0.9–2.2)	2.8 (1.2–6.4)	1.2 (0.6–2.5)	1.6 (0.8–3.3)		X	X			
Chang	1997	1.34 (0.96–1.85)	1.7 (1.00–2.79)	1.585 (0.97–2.58)		X	X	X	X		
Cook	1997	1.7 (1.1–2.5)	1.2 (0.6–2.3)	0.7 (0.4–1.4)	1.8 (1.1–2.8)	X	X	X			
Wong	1999	1.2 (0.7–2.1)	1.4 (0.7–2.7)	1.5 (0.6–4.0)	1.6 (0.6–4.3)	X	X	X			
Mills	2004	1.77 (1.12–2.81)	1.28 (0.62–2.62)	2.56 (0.89–7.39)	0.63 (0.15–2.64)	X	X	X			
Goodman	2008	1.29 (0.82, 2.03)	0.49 (0.20–1.18)	0.82 (0.29–2.30)	1.29 (0.82–2.03)		X		X		
Merritt	2008	1.21 (1.03–1.44)	1.18 (0.81–1.70)	1.10 (0.80–1.52)	1.08 (0.68–1.72)	X	X	X	X		
Gates	2008	1.60 (1.26–2.02)	1.41 (0.97–2.05)	1.28 (0.85–1.92)				X			
Moorman	2009	1.56 (1.13–2.15)	1.19 (0.69–2.06)	0.87 (0.27–1.84)	1.03 (0.52–2.03)		X	X	X		X
Rosenblatt	2011	1.01 (0.69–1.47)	1.53 (0.91–2.57)	1.78 (0.98–3.23)		X	X	X	X		
Lo-Ciganic	2012	1.12 (0.83–1.52)	1.32 (0.74–2.35)	3.03 (1.28–7.16)	1.75 (0.86–3.55)		X		X		
Cramer	2016	1.42 (1.19, 1.69)	1.38 (1.06–1.80)	0.87 (0.53, 1.44)	1.01 (0.65–1.57)	X	X	X	X		
Schildkraut	2016	1.38 (1.03–1.85)				X	X	X			X
Cohort studies											
Gertig	2000	1.26 (0.94–1.69)	0.91 (0.49–1.87)	0.93 (0.53–1.66)		X		X		X	
Gates	2010	1.06 (0.84–1.35)	1.06 (0.66–1.69)	1.50 (0.84–2.66)			X			X	
Houghton	2014	1.16 (0.88–1.53)	1.29 (0.64–2.61)	1.03 (0.47–2.27)	1.04 (0.70–1.54)	X	X	X		X	X
Pooled/meta-analyzed estimates											
Penninkilampi	2018	1.32 (1.22–1.43)	1.35 (1.14–1.60)	1.12 (0.94, 1.33)	1.02 (0.75, 1.39)						
Berge	2018	1.24 (1.15–1.34)	1.15 (0.91–1.39)	0.96 (0.73–1.18)	0.98 (0.72–1.23)						
Taher	2019	1.35 (1.21–1.50)		1.17 (0.82–1.67)							
Terry	2013	1.20 (1.09–1.32)	1.22 (1.04–1.43)	1.09 (0.84–1.42)	1.24 (1.01–1.52)						
O'Brien	2020	1.10 (0.97–1.25)	1.15 (0.83–1.58)	1.03 (0.69–1.54)	1.17 (0.73–1.89)						
Davis, African Americans	2021	1.30 (1.00–1.68)									
Davis, Whites	2021	1.32 (1.13–1.56)									

[a] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62].
[b] Additionally includes data from the Nurses Health Study II (talc data previously unpublished) and the Sister Study [42].
[c] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62] and the Cook County Case-Control Study (talc data previously unpublished).

0.73–1.18) or clear cell (RR = 0.98; 95% CI: 0.72–1.23) [30]. A positive association with serous tumors was again demonstrated in the Taher et al. meta-analysis (OR = 1.35, 95% CI: 1.21–1.50) [31]. Taher et al. observed an elevated but not significant risk associated with mucinous tumors (OR = 1.17, 95% CI: 0.82–1.67). In the Terry et al. pooled analysis, ever genital powder use was associated with serous (OR = 1.20, 95% CI: 1.09–1.32), endometroid (OR = 1.22, 95% CI: 1.04–1.43) and clear cell (OR = 1.24, 95% CI:1.01–1.52) carcinomas, but not mucinous (OR = 1.09, 95% CI: 0.84–1.42) [34].

In the pooled analysis that included updated data from the prospective cohorts, O'Brien et al. observed an elevated but not statistically significant hazard ratio for the association between ever genital powder use and serous ovarian cancers (HR = 1.10, 95% CI: 0.97–1.25) [32]. Estimates were also elevated for endometroid (HR = 1.15, 95% CI: 0.83–1.58) and clear cell (HR = 1.17, 95% CI: 0.73–1.89) carcinomas, but not statistically significant. Ever genital powder use was not associated with mucinous tumors (HR = 1.03, 95% CI: 0.69–1.54). The Davis et al. pooled analyses also reported elevated risk for serous tumors in both African American (OR = 1.30, 95% CI: 1.00–1.68) and white women (OR = 1.32, 95% CI: 1.13–1.56). The other histotypes were not separately evaluated [63].

Overall, these results consistently demonstrate that there is a positive association between talc use and serous ovarian cancers, and possibly also endometroid tumors. The relationship between talc use and the rarer mucinous or clear cell tumor histotypes is more ambiguous, though it is not clear whether this is due to true etiologic differences or because their rarity makes them more difficult to study.

5.3. Associations of genital powder use and ovarian cancer risk by tubal ligation and hysterectomy status

Another key factor in understanding the potentially causal relationship between talc use and ovarian cancer is the concept of patency, defined here as having an unobstructed physical pathway between the genital area and ovaries. The proposed carcinogenic mechanism suggests that talc particles must travel up the reproductive tract (through the vagina, cervix, and uterus) to reach the fallopian tubes and ovaries. As such, it would make sense that women who did not have uteri (i.e. had had a hysterectomy) and/or those who had blocked fallopian tubes (via tubal ligation), would have a markedly reduced risk of developing the disease as a direct consequence of talc use. As described below, many of the existing studies have attempted to look at this in some way. However, most were unable to do so with a clear temporal sequence between hysterectomy/tubal ligation and powder use. For example, it may not be possible to know whether talc was used prior to hysterectomy/tubal ligation or what a woman's combined patency

Table 3
Reported estimates of the association between ever (versus never) powder use and ovarian cancer stratified by hysterectomy and tubal ligation (TL) status, including summary estimates from published meta- and pooled analyses.

Author	Year	Association for ever vs. never talc use		Notes	Taher 2019 meta-analysis	Terry 2013 pooled[a]	O'Brien 2020[b] pooled
		Patent women (no hysterectomy or tubal ligation)	Women with hysterectomy and/or tubal ligation (non-patent)				
Case control studies							
Cramer	1982	2.79 ($p < 0.003$)		compared to 3.28 overall	X		
Whittemore	1988	1.33 (0.88, 2.01)	1.42 (0.75, 2.68)	non-patent estimate based on crude numbers	X		
Harlow	1992	1.7 (1.0–3.0) for 10,000 applications versus none		compared to 1.8 (1.0, 3.0) overall	X		
Rosenblatt	1992	2.4 (1.0–5.8)	0.15 (0.027–0.88)	tubal ligation only; patency estimates based on talc use prior to tubal ligation/ never tubal ligation, non-patent estimate based on time after tubal ligation	X		
Green	1997	1.3 (1.0–1.7)	0.6 (0.5–0.84)	patency estimates based on talc use prior to surgery/ never surgery, non-patent estimate based on time after surgery	X		
Chang	1997	1.11 (0.99–1.24)	1.03 (0.82–1.29)		X	X	
Cook	1997			estimates unchanged after excluding those who used powder after hysterectomy/tubal ligation	X		
Wong	1999	1.2 (0.8–1.6)	0.8 (0.5–1.2)		X		
Mills	2004	1.54 (1.10–2.16) no TL; 1.33 (0.95–1.87) no hyst	0.88 (0.46–1.68) TL; 1.79 (0.91–3.52) hyst		X		
Merritt	2008	>25 years vs. none: 1.29 (1.04–1.58), p-trend =0.02	>25 years vs. none: 1.00 (0.64–1.51); p-trend = 0.61	patency estimates based on talc use prior to surgery/ never surgery, non-patent estimate based on time after surgery	X	X	
Rosenblatt	2011	1.23 (0.93–1.64)		compared to 1.27 (0.97, 1.66) overall	X	X	
Cramer	2016	1.22 (1.04, 1.43)	1.73 (1.31, 2.27)		X	X	
Cohort studies							
Gertig	2000	1.16 (1.01–1.33)	1.07 (0.94–1.20)	updated study-specific results from O'Brien et al.	X		X
Houghton	2014	1.13 (1.01–1.26)	1.11 (0.95–1.30)	updated study-specific results from O'Brien et al.	X		X
Gonzalez	2016	0.85 (0.92–1.39)	1.02 (0.76–1.38)	updated study-specific results from O'Brien et al.	X		X
Pooled/Meta-analyzed estimates							
Taher	2019		1.06 (0.78, 1.42)	compared to 1.06 (0.90–1.25) overall			
Terry	2013	Q5 vs. Q1 of cumulative applications: 1.36 (1.18–1.57)		Limiting analysis to those exposed prior to surgery (or never surgery) made "no substantive difference" in results			
O'Brien	2020	1.13 (1.01–1.26)	0.99 (0.86–1.15)				
Davis[c]	2021	1.27 (1.09–1.48)	1.42 (1.17–1.72)				

[a] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62]; the Hawaii Ovarian Cancer Study [43]; the North Carolina Ovarian Cancer Study [53]; the Hormones and Ovarian Cancer Prediction Study [50].
[b] Additionally includes data from the Nurses Health Study II (talc data previously unpublished) and the Sister Study [42].
[c] Includes only Women's Health Initiative [48] from table. Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62], the Cook County Case-Control Study (talc data previously unpublished), North Carolina Ovarian Cancer Study [53] and the African-American Cancer Epidemiology Study [28].

and talc use status was during key windows of susceptibility (e.g. menopause).

In their pooled analysis of 8 case-control studies, Terry et al. found that after excluding those who first started using genital powder after hysterectomy or tubal ligation, results were similar to the overall analysis (Table 3; OR = 1.36, 95% CI: 1.18–1.57 for the 4th versus 1st quartile of cumulative number of lifetime talc applications; compared to original overall estimate OR = 1.32, 95% CI: 1.16–1.52) [34]. The only meta-analysis to explore this issue was Taher et al., who reported an inverse association between talc and ovarian cancer among those who had had tubal ligation (OR = 0.64, 95% CI: 0.45–0.92) [31]. When they examined studies that reported estimates from participants with a history of either hysterectomy or tubal ligation, the meta-analyzed estimate was close to null (OR = 1.06, 95% CI: 0.78–1.42). Davis et al. reported similar estimates when analyses were restricted to women with patent reproductive tracts (OR = 1.27, 95% CI: 1.09–1.48) versus those with a history of tubal ligation or hysterectomy (OR = 1.42, 95% CI: 1.17–1.72; p-for-heterogeneity = 0.31) [63].

The prospective studies did not systematically collect details on timing of genital powder use relative to the age at which women underwent hysterectomy or tubal ligation [32]. However, in those who had patent reproductive tracts at enrollment, a history of genital powder use was associated with an increased risk of developing incident ovarian cancer (HR = 1.13, 95% CI: 1.01–1.26). This association was null among women who did not have patent reproductive tracts at enrollment (HR = 0.99, 95% CI: 0.86–1.15).

Given the difficulties with establishing a clear sequence of events in the genital powder use relative to hysterectomy or tubal ligation, especially in the case-control studies, the interpretation of these findings is quite difficult. However, the results of the prospective studies support the hypothesis that the positive association between genital powder use and ovarian cancer may be limited to women with patent reproductive tracts.

5.4. Associations of genital powder use and ovarian cancer risk in diverse populations

As previously mentioned, Davis et al. conducted a pooled analysis examining the association between genital powder use and ovarian cancer in the OCWAA consortium [63], which only included studies with large samples of African-American women. Consistent with previously observed trends, African American women in the included studies were more likely to report ever having used genital powder (34% of African-American non-cases versus 31% of White non-cases), but effect estimates were similar between the two racial groups (OR = 1.22, 95% CI: 0.97–1.53 in African American women and OR = 1.37, 95% CI: 1.1–1.57 in White women). In analyses limited to high grade serous tumors, Davis et al. reported elevated associations for both African American (OR = 1.30. 95% CI: 1.00–1.68) and White (OR = 1.32, 95% CI: 1.13–1.56) women. Non-serous tumors were positively associated with powder use in White women (OR = 1.38, 95% CI: 1.15–1.66), but not African American women (OR = 1.08. 95% CI: 0.78–1.51).

5.5. Association of genital powder use and uterine cancer

The shared etiology of ovarian and uterine cancer subtypes warrant evaluation of presumed and established ovarian cancer risk factors in uterine cancer studies. Genital powder has easier access to the uterine lining compared to the fallopian tubes and the ovarian surface. On the other hand, menstruation could clear genital powder from the surface of the uterus, thereby mitigating its influence. Several studies have evaluated the association of genital powder use and uterine cancer, including one case-control study [64] and three cohort studies [65–67]. Updated data from the three cohorts plus the Nurses' Health Study II were combined in a uterine-cancer specific pooled analysis [26].

The case-control study reported no association between perineal talc use and endometrial cancer (OR = 0.88, 95% CI: 0.68–1.14) [64]. Findings from the pooled analysis were also null (HR = 1.01, 95% CI: 0.94–1.09), except for a possible increased risk among long-term users (>20 years; HR = 1.12, 95% CI: 0.96–1.31). There was no evidence for heterogeneity by endometrial cancer subtype.

6. Conclusion

When assessing the complex relationship between genital powder use and ovarian cancer, three important related questions need to be addressed: 1. Is there an association between genital powder and ovarian cancer risk? 2. If there is an association, what is the underlying causal factor? 3. If there is an association, what is the clinical and public health relevance? The epidemiological data on the association between powder use and ovarian cancer risk have varied by study type. Recent systematic reviews and meta-analyses that included case-control data reported elevated ovarian cancer risk among powder users relative to non-users, with odds ratios ranging from 1.22 to 1.32. Concern has been raised that this association could be at least somewhat attributable to recall bias, which would occur if ovarian cancer patients were more likely to report body powder use compared to controls [29].

Because cohort studies assess exposure before disease occurs, they are not subject to recall bias. Individual cohort studies have not shown statistically significant associations between powder use and ovarian cancer risk, but many cohort studies are limited by low ovarian cancer case numbers and limited exposure assessments. In a recent pooled cohort analysis with a large number of cases, ever use of genital powder was positively associated with ovarian cancer, but the hazard ratio did not reach statistical significance. However, a pre-specified sub-analysis limited to women who had not had a hysterectomy or tubal ligation showed a statistically significant positive association (HR = 1.13). Taken together, the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer, which may be limited to women with patent reproductive tracts. Data from a large case-control study suggested that associations between talc use and ovarian cancer risk were largely confined to premenopausal women and postmenopausal women who used hormone therapy [39]. This could indicate that estrogen may be an effect modifier of the talc-ovarian cancer association.

The inability to differentiate between different types of powder and their respective ingredients in epidemiological studies makes it challenging to identify factors responsible for the observed associations. Since talc is a major component in many body powders, it has long been proposed as a causal factor. However, the experimental and animal carcinogenicity data for talc are limited and inconclusive, and there are currently no good animal or experimental models of ovarian carcinogenesis that could be used to more directly test biological effects of talc [1]. Asbestos contamination of talc was proposed as an explanation for some of the initially observed associations between powder use and ovarian cancer, and recent findings of asbestos contamination in cosmetic products suggest that asbestos could have continued to play a role. Data on other possibly carcinogenic contaminants of talc, such as quartz, are very scarce. Other components of body powder, including corn starch, could also possibly play a role in carcinogenesis by inducing inflammation in the reproductive tract, but carcinogenicity data are lacking. Confounding by indication may explain some of the observed associations. This would occur if women with hormonal or inflammatory exposures or conditions that are associated with ovarian cancer were also more likely to use powder in the genital area. However, there is currently no data supporting such an effect. In summary, we currently do not understand the causal factors that underly the observed weak associations between genital powder use and ovarian cancer risk.

Independent of the underlying cause, the association between powder use and ovarian cancer risk is weak. The low relative risk translates to a very low absolute risk increase, given the rarity of ovarian cancer. In the pooled cohort analysis by O'Brien et al., the estimated increase in ovarian cancer risk by age 70 was 0.09% (95% CI: −0.02-0.19%) for all users of body powder and 0.22% (95% CI: 0.02–0.42%) for body powder users with patent reproductive tracts [32]. Given the inability to attribute a clear causal factor to the observed associations, the lack of a good experimental model, the lack of a specific biomarker for powder-related carcinogenesis, and the inability to rule out confounding by indication, it is difficult to conclude that the observed associations are causal. Furthermore, given the widespread use of powders and the rarity of ovarian cancer, the case for public health relevance is limited.

Future work on understanding the association of powder use and ovarian cancer risk should focus both on existing data and new studies. Given that the association from case-control studies may be exaggerated by recall bias and the association from cohort studies may be underestimated because of limited exposure information and attenuation in effects over time since exposure assessment, the association probably lies between these estimates. A systematic bias assessment could attempt to account for these biases and lead to a more accurate risk estimate. Existing studies may have collected more detailed exposure information, particularly on timing of powder use and brand names that could allow investigators to revisit the role of possible asbestos contamination of cosmetic talc products. Further, data on additional medical conditions that may be related both to ovarian cancer risk and powder use may be available in these studies, allowing for further evaluation of confounding by indication. Future studies should expand on the assessment of body powder use, with an extended focus that captures data on different formulations, including talc-free brands and improved exposure quantification. Ideally, this would also include careful consideration of differences in product use across different racial/ethnic groups, given the observed higher use of genital powder among African American women [63]. Biological and experimental studies on potential mechanisms of powder-related carcinogenesis should also focus more on extra-ovarian cells of origin, particularly in the fallopian tubes. Further, biological studies should evaluate other components of body powders, such as corn starch, that may cause inflammatory reactions in the genital tract and the fallopian tubes. Despite the limitations of current experimental and animal models that complicate evaluating the full carcinogenic process, the effects of body powder components on inflammation in various areas of the genital tract could provide important data on intermediate endpoints that could explain potential carcinogenic mechanisms.

Use of talcum powder has decreased substantially in the US over the last decades [68]. Following the recent reports on asbestos contamination of talc products, the cosmetic industry has moved away from using talc in their products and major brands of talcum powder have been removed from the market. Given the weak observed associations and the uncertainty of the underlying causes, current recommendations about body powder use remain vague. For example, the American Cancer Society states that “Until more information is available, people concerned about using talcum powder may want to avoid or limit their use of consumer products that contain it.” [69] Given the uncertainty about the role of other powder ingredients in the observed associations and continued widespread use of body powder around the world, we should continue to evaluate the health effects of genital powder use, as well as the public health messaging related to powder use.

Author contributions

Nicolas Wentzensen: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft, review & editing. *Katie O'Brien*: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft, review & editing.

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Declaration of Competing Interest

The authors do not report a conflict of interest.

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